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EXAMINER

SISSON, BRADLEY L

ART UNIT PAPER NUMBER

1634

DATE MAILED: 08/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/937,784

Applicant(s)

DENSHAM, DANIEL HENRY

Examiner

Bradley L. Sisson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 26 May 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 7-20 and 22 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 7-20 and 22 is/are rejected.
- 7) ☒ Claim(s) 13 and 20 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>31 May 2006</u> . | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Specification***

1. The objection to the specification is hereby withdrawn.

### ***Claim Objections***

2. Claims 13 and 20 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 7, from which claim 13 depends, and claim 14, from which claim 20 depends, have been amended so to recite that the enzymes are immobilized. Given this limitation, it is not clear how claims 13 and 20 further limit claims 7 and 14, respectively.

### ***Claim Rejections - 35 USC § 112***

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 7-20 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the

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claimed invention. Attention is directed to the decision in *University of Rochester v. G.D. Searle & Co.* 68 USPQ2D 1424 (Fed. Cir. 2004) at 1428:

To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563; see also *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that “the inventor invented the claimed invention”); *In re Gosteli*, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) (“the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed”). Thus, an applicant complies with the written-description requirement “by describing the invention, with all its claimed limitations, not that which makes it obvious,” and by using “such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention.” *Lockwood*, 107 F.3d at 1572.

5. For convenience, claims 7, 14, and 22, the only independent claims both pending and under consideration on the merits, are reproduced below.

**Claim 7 (Currently amended):** A method for sequencing a polynucleotide, comprising the steps of:

- (i) ~~reacting a~~ an isolated target polynucleotide with ~~a an~~ an immobilised helicase enzyme or a primase enzyme, under conditions suitable for enzymic activity; and
- (ii) ~~applying radiation to the reaction of step (i); and~~
- ~~(4)(iii)~~ detecting the interaction between the enzyme and the nucleotide on the target polynucleotide, to thereby determine the sequence of the target polynucleotide, the detection being carried out by measuring a change in, or absorption of, the applied radiation that occurs during the interaction.

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**Claim 14 (Currently amended):** A method for sequencing a polynucleotide, comprising the steps of:

- (i) reacting a an isolated target polynucleotide with a an immobilized helicase enzyme and a an immobilized primase enzyme under conditions suitable for enzyme activity; and
- (ii) applying radiation to the reaction of step (i); and
- (i)(iii) detecting the interaction between the enzymes and the nucleotide on the target polynucleotide, to thereby determine the sequence of the target polynucleotide, the detection being carried out by measuring a change in, or absorption of, the applied radiation that occurs during the interaction.

**Claim 22 (Currently amended):** A method for sequencing a polynucleotide, comprising the steps of:

- (i) reacting a an isolated target polynucleotide with a an immobilized helicase enzyme under conditions suitable for enzyme activity; and
- (ii) applying radiation to the reaction of step (i); and
- (i)(iii) detecting the interaction between the helicase enzyme and the nucleotide on the target polynucleotide, to thereby determine the sequence of the target polynucleotide, the detection being carried out by measuring a change in, or absorption of, the applied radiation that occurs during the interaction.

6. For purposes of examination, the claimed method has been interpreted as encompassing the simultaneous sequencing a multiple nucleic acids in a single sample. The claimed method has also been interpreted as sequencing an unknown target nucleic acid when it is present in a mixture of nucleic acids.

7. The claimed method has been interpreted as encompassing the application of any intensity level of radiation for any duration, and where the nucleotide sequence of a nucleic acid of any length, up to and including intact chromosomes, is reproducibly determined.

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8. The claimed method fairly encompasses performing the method where the enzyme is immobilized and unincorporated reactants are not removed from the reaction site.
9. A review of the disclosure finds but one example, and then the statement that “DNA sequencing was conducted by the method described in WO-A-99/0515, using the apparatus shown in Fig. 1, but using only one focusing assembly (5) for pulsing monochromatic light into the cell.”
10. A review of WO-A-99/0515 find the following disclosure at page 14, bridging to page 15:

#### DNA Sequencing

Figure 1 shows a SPR sensing system and fluidic cell (7), having a means for applying electromagnetic radiation (1) to a sensor chip (2) with an immobilised polymerase enzyme (3) at the sensor surface, an inlet (4) for introducing the different nucleotides into the cell and two focusing assemblies (5) and (6) for pulsing monochromatic light into the cell. The different nucleotides are introduced into the fluidic cell (7) at a flow rate of 30  $\mu\text{l}/\text{min.}$ , at a temperature of 25°C and a data collection rate of 10 Hz. As the nucleotides pass the focusing assembly (5), monochromatic light at a wavelength of 260 nm is pulsed to remove the blocking group at the 5' position. The nucleotides then flow over the sensor chip (2) and contact the target polynucleotide/ polymerase complex (3) which is held in place by the  $\beta$ -dimer sub-assembly. Since the 3' position on the primer sequence is free to react, polymerisation may take place as a nucleotide is incorporated onto its complement on the target polynucleotide. This incorporation is then detected by the monochromatic p-polarised light of the SPR device. No further polymerisation occurs, since the incorporated nucleotide has a blocking group at the 3, position. Monochromatic light of wavelength 360 nm is then pulsed by the focusing assembly (6) at the site of polymerisation. The high flow rate in the fluidic cell ensures that nucleotides not bound to the polymerase are removed from the cell before sufficient energy has been absorbed to release their 3' blocking groups.

11. As seen above, only one form of radiation has been exemplified, and then it was monochromatic light of 360 nm. It is further noted that the unincorporated nucleotides were removed from the area of the reaction due to a “high flow rate in the fluidic cell” before they could have absorbed sufficient energy causing the release of their 3' blocking groups. Clearly,

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the example does not teach nor reasonably suggest performing the reaction where unincorporated reactants are retained, and where other forms and wavelengths of radiation are used, and where the detection is based upon detection means other than surface plasmon resonance.

12. The specification of the instant application, and the relevant portion of the WO document does not teach or even reasonably suggests practicing the now claimed method where a helicase of primase is used.

13. The specification has not been found to teach using multiple types of enzymes in the context of a single assay (limitation of claims 14-20), or for that matter, the use of an enzyme other than a “polymerase enzyme.” Further, neither the instant disclosure nor the sequencing method disclosed in the WO document fairly teach in such full, clear, and concise language how the claimed method is to be practiced with surface plasmon resonance, nuclear magnetic resonance. While the specification may provide literal support for other theoretical or potential embodiments, the disclosure provided lacks the detailed teaching that reasonably suggests that applicant had possession of these alternative embodiments.

14. In view of the breadth of the claims, the limited disclosure provided, and the general absence of the requisite “full, clear, concise and exact” language required under 35 USC 112, first paragraph, the specification is deemed to not provide an adequate written description of the full genus of the claimed invention.

15. It appears that applicant is attempting to satisfy the written description requirement of 35 USC 112, first paragraph, through obviousness. Obviousness, however, cannot be relied upon for satisfaction of the written description requirement. In support of this position, attention is directed to the decision in *University of California v. Eli Lilly and Co.* (Fed. Cir. 1997) 43

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USPQ2d at 1405, citing *Lockwood v. American Airlines Inc.* (Fed. Cir. 1997) 41 USPQ2d at 1966:

Recently, we held that a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention.

16. For the above reasons, and in the absence of convincing evidence to the contrary, claims 7-20 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Response to arguments

At page 6, bridging to page 7 of the response received 26 May 2006, hereinafter the response, argument is presented that “it is the applied radiation that is detected.” This argument has not been found persuasive, as claim 14 requires one to measure “a change in, or absorption of, the applied radiation.” Simply measuring the radiation at a given point in time, with no reference point to determine change or absorption would not result in any meaningful information.

At page 7 of the response argument is presented that the claimed method does not involve unincorporated nucleotides as one is simply “monitoring a helicase enzyme as it unwinds a DNA helix [which] allows the DNA to be sequenced.”

The above argument has not been found persuasive, as the method of claim 14 is not predicated on measuring only a helicase, rather, one is using a primase and a helicase. Clearly, the instant specification does not teach which changes in absorption are to be correlated with a specific nucleotide, and how one nucleotide is to be distinguished over that of another, especially when multiple sequences may be sequenced at the same time. Furthermore, the document upon which applicant had predicated the enablement/written description support does not teach the claimed



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method, much less reasonably suggest how it is to be performed, regardless of radiation or detection means employed.

17. At page 8 of the response applicant's representative asserts:

The subject specification provides relevant identifying characteristics sufficient to describe the claimed invention in such full, clear, concise and exact terms that one of ordinary skill in the art would recognize that the applicant was in possession of the claimed invention.

18. A review of applicant's argument, however, fails to find any showing of evidence, e.g., page and line number, where such a compliant description is to be found. Therefore, and in the absence of convincing evidence to the contrary, the rejection is maintained.

19. Claims 7-20 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, e.g., *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining

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whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

20. As set forth above, each of the three independent claims require one to measure a change in, or absorption of, radiation that occurs during the interaction of "a target polynucleotide with a helicase enzyme or a primase enzyme", or in the case of claim 14, both enzymes are used. It is noted with particularity that no restriction is placed on the form, duration, wavelength, or intensity of radiation be inputted to the reaction, rather, only that a change, if any, be measured. The specification, however, does not fully enable the claims' scope.

21. As presently worded, the claimed method also fairly encompasses determining the nucleotide sequence of any and all chromatin found within any human cell, e.g., the human genome, mRNA, tRNA, rRNA as well as mitochondrial DNA and RNA, when the nucleic acid is still within a cell and the cell is subjected to radiation such that that associated with daylight as well as when exposed to any other form of electromagnetic radiation. The specification, however, is silent as to how such embodiments could be accomplished.

22. Additionally, the claimed method fairly encompasses determining the complete nucleotide sequence of any nucleic acid, e.g., intact chromosomes, when no radiation is used and accordingly, there is no change in radiation emission or absorption.

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23. Further, the claimed method has been construed as encompassing performing the claimed method where all reactants are floating in solution and the period for enzymatic activity is intermittent or transient.

24. Likewise, the claimed method fairly encompasses performing the method where the enzyme is immobilized and unincorporated reactants are not removed from the reaction site.

25. The claimed method fairly encompasses determining the nucleotide sequence of a limitless number of different “nucleic acids” in a simultaneous manner, where the “nucleic acid” is of any length and is in the same reaction area.

26. A review of the disclosure finds but one example, and then the statement that “DNA sequencing was conducted by the method described in WO-A-99/0515, using the apparatus shown in Fig. 1, but using only one focusing assembly (5) for pulsing monochromatic light into the cell.” WO-A-99/0515 teaches at page 14, bridging to page 15:

#### DNA Sequencing

Figure 1 shows a SPR sensing system and fluidic cell (7), having a means for applying electromagnetic radiation (1) to a sensor chip (2) with an immobilised polymerase enzyme (3) at the sensor surface, an inlet (4) for introducing the different nucleotides into the cell and two focusing assemblies (5) and (6) for pulsing monochromatic light into the cell. The different nucleotides are introduced into the fluidic cell (7) at a flow rate of 30  $\mu\text{l}/\text{min.}$ , at a temperature of 25°C and a data collection rate of 10 Hz. As the nucleotides pass the focusing assembly (5), monochromatic light at a wavelength of 260 nm is pulsed to remove the blocking group at the 5' position. The nucleotides then flow over the sensor chip (2) and contact the target polynucleotide/ polymerase complex (3) which is held in place by the  $\beta$ -dimer sub-assembly. Since the 3' position on the primer sequence is free to react, polymerisation may take place as a nucleotide is incorporated onto its complement on the target polynucleotide. This incorporation is then detected by the monochromatic p-polarised light of the SPR device. No further polymerisation occurs, since the incorporated nucleotide has a blocking group at the 3' position. Monochromatic light of wavelength 360 nm is then pulsed by the focusing assembly (6) at the site of polymerisation. The high flow rate in the fluidic cell ensures that nucleotides not bound to the polymerase are removed from the cell before sufficient energy has been absorbed to release their 3' blocking groups.

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27. While the specification states that “DNA sequencing was conducted by the method described in WO-A-99/-5315” (specification at page 7, line 26), applicant’s representative asserts that DNA sequencing was not conducted in such a manner, but rather, “is based on the realization that monitoring a helicase enzyme as it unwinds a DNA helix allows the DNA to be sequenced.” Clearly, the specification does not enable such a method, and the document being relied upon for enablement also does not teach a reproducible method to practice the now claimed method. In short, the specification does not teach the reactants and reaction conditions under which the full scope of the claims can be practiced. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

“ ‘[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.’ *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) (‘[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.’). ”

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“Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that ‘a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.’) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. “It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling

disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research. (Emphasis added)

28. For the above reasons, and in the absence of convincing evidence to the contrary, claims 7-20 and 22 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Response to argument

29. At page 9 of the response applicant's representative asserts the claimed method does not involve the incorporation of nucleotides, and as such, arguments to such an issue do not relate to the claimed invention.

30. The above argument has been fully considered and has not been found persuasive, as the claimed method does not exclude the use of nucleotides that are free in solution. Further, a review of the specification of the instant application finds at page 6 the statement that "The following Example illustrates the invention." Page 7, bridging to page 8 of the specification is the only part of the specification that is directed to "DNA Sequencing." A review of the method disclosed therein plainly states: "DNA sequencing was conducted by the method described in WO-A-99/05315, using the apparatus of Fig. 1, but using only one focusing assembly (5) for pulsing monochromatic light into the cell." A review of the specification further states that ATP

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is being introduced into the active site of the helicase. Clearly, there must be ATP present in the solution.

31. The aspect of measuring absorption of radiation by the helicase is also not supported by the disclosure. As seen at page 8 of the specification which states in part: "The conformational change associated with the base movement s then detected by the p-polarized light of the SPR device which is wavelength-modulated in order to produce an SPR spectrum."

32. The specification is silent as to what values associated with "base movement" are to be equated with a specific base being peasant in the target nucleotide sequence. The specification is also silent as to what these values are for each of the forms of radiation used, accounting for intensity and duration, the forms of helicase used, and the means of measuring as recited in each of claims 9-12 and 15-19.

33. At page 9, second paragraph, of the response, applicant's representative requests clarification regarding "the statement in item 33 at page 10 of the Office Action."

34. For convenience, the item is reproduced below.

35. "The claimed method fairly encompasses performing the claimed method where all reactants are floating in solution and the period for enzymatic activity in intermittent or transient."

36. The above statement was setting out for the record how the claim was being construed. In one instance, the claim had been interpreted as having all reactants in solution. By way of applicant's amendment, it is now clear that the primase or helicase (claims 7-13), or the primase and helicase are both immobilized to some unidentified object.

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37. The above passage also articulated that the enzymatic activity may not be continuous, but rather, discontinuous. Support for this interpretation is based in part on the specification stipulating that the substrate was presented in a “transient” manner (see specification at page 8, second paragraph).

38. At page 9 of the response argument is presented that there is no reason to remove reactants from the reaction site.

39. The above argument is not found persuasive as the specification teaches but a single method of practicing the invention and then the specification teaches explicitly of “transiently” introducing a solution containing 0.5 mM NPE-caged ATP. The aspect of “transiently” introducing the substrate speaks directly to the substrate being present for one part of the experiment and not present for another. Accordingly, and in the absence of convincing evidence to the contrary, the specification is deemed to not support the position of using uncaged nucleotides and then only having the nucleotides present on a “transient” basis.

#### ***Double Patenting Rejection***

40. The double patenting rejection has been withdrawn.

#### ***Conclusion***

41. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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42. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

43. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

44. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

45. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would



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like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

A handwritten signature in black ink, appearing to read "B. L. Sisson".

Bradley L. Sisson  
Primary Examiner  
Art Unit 1634

BLS